

How Valid Are the Rates of Down Syndrome Internationally? Findings from the International Clearinghouse for Birth Defects Surveillance and Research

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Rates of Down syndrome (DS) show considerable international variation, but a systematic assessment of this variation is lacking. The goal of this study was to develop and test a method to assess the validity of DS rates in surveillance programs, as an indicator of quality of ascertainment. The proposed method compares the observed number of cases with DS (livebirths plus elective pregnancy terminations, adjusted for spontaneous fetal losses that would have occurred if the pregnancy had been allowed to continue) in each single year of maternal age, with the expected number of cases based on the best-published data on rates by year of maternal age. To test this method we used data from birth years 2000 to 2005 from 32 surveillance programs of the International Clearinghouse for Birth Defects Surveillance and Research. We computed the adjusted observed versus expected ratio (aOE) of DS birth prevalence among women 25–44 years old. The aOE ratio was close to unity in 13 programs (the 95% confidence interval included 1), above 1 in 2 programs and below 1 in 18 programs ($P < 0.05$). These findings suggest that DS rates internationally can be evaluated simply and systematically, and underscores how adjusting for spontaneous fetal loss is crucial and feasible. The aOE ratio can help better interpret and compare the reported rates, measure the degree of under- or over-registration, and promote quality improvement in surveillance programs that will ultimately provide better data for research, service planning, and public health programs. © 2010 Wiley-Liss, Inc.

Key words: Down syndrome; epidemiology; prevalence; validity; registries

INTRODUCTION

Over the last several decades, national and international efforts have led to the establishment of many birth defect registries and surveillance programs worldwide [Dolk, 2005; Botto et al., 2006].

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Although their specific goals vary, a shared objective of these programs is to monitor the occurrence of birth defects and their changes over time. Monitoring has many uses. It can detect clusters or epidemics of birth defects, document the effectiveness of preventive interventions (as in the case of folic acid fortification to prevent neural tube defects), and help estimate the burden of disease when developing public health priorities. The usefulness of such information is enhanced when shared by the program within a country [Canfield et al., 2006; Kirby and Mai, 2006] or internationally [Dolk, 2005; Botto et al., 2006], as promoted by the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), which has member programs from North America, South America, Europe, Middle-East, Far East, and Oceania [Botto et al., 2006].

For many birth defects, and for Down syndrome (DS) in particular, rates by country and surveillance program can vary considerably. DS is in fact one of the most common birth defect evaluated by surveillance programs [Stoll et al., 1994; Ilyasu et al., 2002; Dolk et al., 2005; Métneki and Czeizel, 2005; Mosquera Tenreiro et al., 2009], and its variation raises the issue of the validity of the findings and the extent that the variation reflects problems in diagnosis, ascertainment, and registration. In studies of DS, validation typically focuses on precision of clinical diagnosis or on completeness of ascertainment and reporting. Validating the clinical diagnosis was not the specific aim of this study, and would typically require evaluating the completeness of cytogenetic diagnosis or the clinical precision of expert clinical geneticists. In this study we focused on a crucial epidemiologic aspect of validation, the completeness of ascertainment and reporting. In a more general project to evaluate the validity of birth defect rates, we focused on such epidemiological validation of DS rates for several reasons. First, as mentioned, DS is one of the most common birth defects monitored by many programs. Second, many cases can be diagnosed clinically in the newborn period, more easily than for many common structural birth defects (e.g., some heart and kidney malformations), so that validity issues in rates of DS may suggest perhaps even greater challenges in the ascertainment of other birth defects. Third, it is recognized that in many countries, elective terminations of pregnancy have a considerable impact on the birth prevalence of many birth defects including DS (particularly as maternal serum screening is increasingly recommended). Finally, data published over the years suggest that rates of DS, once one accounts carefully for spontaneous fetal losses after a prenatal diagnosis (SFL) and maternal age, are fairly stable and constant across years and countries [Carothers et al., 1999]. This fact provides a robust basis to generate expected rates for DS, and support the choice of DS when trying to assessing the validity of rates in a surveillance program.

A common approach to validation of DS rates has been to use active ascertainment from additional external data sources, with or without statistical methods such as capture–recapture [Hook and Regal, 1995; Campbell et al., 2002; Wang et al., 2006; Melve et al., 2008; Savva and Morris, 2009]. This approach, however, can be impractical for many programs, either because it can be costly and difficult to perform or because high-quality external and independent data sources may be unavailable.

We describe here in detail a simple and inexpensive method to evaluate the validity of DS rates, which can be used in many surveillance programs in developed and developing countries. We used this method to examine rates from a recent cohort of births with DS from 32 birth defects surveillance programs worldwide.

METHODS

Data Sources

We used data on DS collected by surveillance programs that are members of the ICBDSR. For most programs we evaluated births for the period 2001–2005, with the exception of Chile Maule (time period, 2002–2005), Malta (1999–2007), USA Atlanta (2000–2004), and USA Utah (2001–2006). Data on DS and on total births for these years were requested by single-year maternal age intervals

and by birth outcome (stillbirths and livebirths). For elective terminations of pregnancy after a prenatal diagnosis of DS (thereafter named ETOP), where these were legal, the gestational age at termination (<16 weeks; 16 weeks or more) was also requested. Six surveillance programs (Chile Maule, Italy Campania, Italy Lombardia, Italy Sicilia, Japan JAOG—Japan Association Obstetric and Gynecology, Russia Moscow) could provide the distribution by single year of maternal age for the cases of DS, and by 5-year interval for all births. In such cases, for the three Italian programs (Italy Campania, Italy Lombardia, Italy Sicilia) we estimated the maternal age distribution of total births by single year within each 5-year age group using the regional birth distribution given by the Italian National Institute of Statistics (ISTAT, 2009), whereas for Chile Maule, Japan JAOG, and Russia Moscow we used 5-year maternal age intervals.

The main characteristics of the surveillance programs are summarized in Table I. Additional details of these surveillance programs (e.g., reporting, coding) are available from the annual reports of the ICBDSR [2009] and the National Birth Defects Prevention Network [NBDPN, 2006], from the EUROCAT—European Surveillance of Congenital Anomalies website (<http://www.eurocat.ulster.ac.uk/>, Nov 27, 2009), and from selected publications from individual surveillance programs [Mutchinick et al., 1988; Czeizel, 1997; Irgens, 2000; Castilla and Orioli, 2004; De Vigan et al., 2005; Feldkamp et al., 2005; Wertelecki, 2006; Correa-Villasenor et al., 2003; Lowry et al., 2007; Zhuchenko et al., 2008].

Study Design

The goal of the study was to estimate the observed versus expected number of DS cases among livebirths. With perfect ascertainment and in the absence of ETOP, the *expected* number of DS cases in a population can be directly inferred from the maternal age specific rates of livebirth with DS published by Hecht and Hook [1996], specifically the “derived rates” in Table 2 of their article, which are based on studies judged by the authors to have “near complete” ascertainment of livebirth cases of DS. These rates are modeled rates and are very similar to those computed by Bray et al. [1998] and by Morris et al. [2003]. Applying these rates to the maternal age distribution of the underlying population would provide a first estimate of the expected number of cases of DS in that population.

Computing the number of *observed* livebirths with DS in a registry would be straightforward, except for the presence of ETOP. Summing all livebirths and ETOP is only a first approximation. ETOP with DS cannot be directly summed to the livebirth cases because some of the ETOP would have been lost as SFL if they had been allowed to continue; a further adjustment is required. We used the estimated rates of SFL in DS by single year of maternal age (25–44 years) published by Savva et al. [2006] in their Table 1, and applied these to the ETOP with DS reported in each surveillance program. SFL rate between the time of chorionic villus sampling (CVS) and birth were used to adjust for ETOP before 16 weeks gestation; SFL rate between amniocentesis and birth were used to adjust for ETOP at 16 weeks or more. The new adjusted number of observed cases can then be computed (Table II, fourth column), to include livebirths plus the fraction of ETOP that would have ended

TABLE I. Surveillance Programs Members of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) and Their Main Methodological Characteristics

Surveillance programs	Coverage	Elective terminations of pregnancy (ETOP)	Maximum age for ascertainment or registration	Source of ascertainment: livebirths, stillbirths, and ETOP	Criteria defining stillbirths	Clinical diagnosis accepted	Informed consent for registration of cases requested
Australia Victoria	PP1	P, R	15 years	M w/C	20 weeks or 400 g	No	No
Canada Alberta	RP	P, R	1 year	M w/C	20 weeks or 500 g	Yes	No
Chile Maule	H	NP	Hosp. discharge	S	500 g	Yes	No
Czech Republic	RP	P, R	15 years	M w/C	28 weeks or 1,000 g	No	No
Finland	RP	P, R	Unlimited	M w/C	22 weeks or 500 g	Yes	No
France REMERA	RP	P, R	18 months	M w/C	22 weeks	No	Yes
Germany Saxony Anhalt	PP2	P, R	1 year	M	500 g	Yes	Yes
Hungary	RP	P, R	1 year	M w/C	24 weeks or 500 g	Yes	No
Iran TRoCA	H	P, NR	1 year	M	20 weeks or 400 g	Yes	No
Ireland Dublin	RP	NP	5 years	M w/C	24 weeks or 500 g	Yes	No
Israel BDSP	H	P, R	3–7 days	S	20 weeks or 500 g	No	No
Italy Campania	PP1	P, R	1 year	S	180 days	Yes	No
Italy Emilia Romagna	PP1	P, R	1 week	S	180 days	No	No
Italy Lombardia	RP	P, R	1 year	M	180 days	Yes	No
Italy Sicilia	H	P, R	1 year	M	180 days	Yes	No
Italy Toscana	RP	P, R	1 year	M	180 days	No	No
Japan JAOG	H	P, NR	Hosp. discharge	S	22 weeks	Yes	Yes
Malta	RP	NP	1 year	M	20 weeks	Yes	No
Mexico RYEMCE	H	NP	Hosp. discharge	S	20 weeks or 500 g	Yes	Yes
Northern Netherlands	RP	P, R	15 years	M w/C	24 weeks	No	Yes
Norway	RP	P, R	1 year	S	12 weeks	Yes	No
Russia Moscow	RP	P, R	1 year	M w/C	28 weeks	No	No
Slovak Republic	PP1	P, R	1 year	S	28 weeks or 1,000 g	No	No
South America ECLAMC	H	NP	Hosp. discharge	S	500 g	Yes	Yes
Sweden	RP	P, R	1 year	M w/C	22 weeks	No	No
Ukraine	RP	P, R	1 month	M w/C	500 g	Yes	No
USA Atlanta	RP	P, R	6 years	M w/C	20 weeks	Yes	No
USA California	RP	P, R	1 year	M w/C	20 weeks	Yes	No
USA Texas	RP	P, R	1 year	M w/C	20 weeks	Yes	No
USA Utah	RP	P, R	5 years	M w/C	20 weeks	Yes	No
Wales	RP	P, R	1 year	M w/C	24 weeks	Yes	No
Western Australia	PP1	P, R	6 years	M w/C	20 weeks or 400 g	Yes	No

ECLAMC, Latin-American Collaborative Study on Congenital Anomalies; IBDSR, Israel Birth Defects Surveillance Program; JAOG, Japan Association Obstetric and Gynecology; REMERA, Rhone-Alps Registry of Congenital Anomalies; RYEMCE, Mexican Registry and Epidemiological Surveillance of Congenital Malformations; TRoCA, Tabuz Registry of Congenital Anomalies.

Coverage: RP, resident population, when it includes only subjects born to mothers with the residency during gestation in the area covered by the registry, wherever the delivery took place, and it excludes all the subjects born to non-resident mothers that delivered in the area covered by the registry. PP1, present population, when it includes all subjects born to mothers that delivered in the area covered by the registry, wherever they had the residency during gestation. PP2, present population excluding subjects born to mothers that delivered in the area covered by the registry but had the residency out of the area. The registry does not cover subjects born outside the area of mothers resident in the area. H, hospital based, when it includes only a proportion—even near to 99%—of all subjects delivered in the area covered by the registry.

Elective terminations of pregnancy after prenatal diagnosis (ETOP): P, permitted by country's legislation; NP, not permitted; R, reported; NR, not reported.

Source of ascertainment: S, single source; M, multiple sources; M w/C, multiple source including Cyto Labs.

TABLE II. Down Syndrome Adjusted Observed–Expected (aOE) Ratio for the Maternal Age 25–44 years by International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) Surveillance Programs (2001–2005)

Surveillance program	Total births	Observed total cases ^a	Observed LB cases adj ^b	Expected LB cases	aOE	95% CI
Chile Maule ^c	30,250	106	105	82.4	1.27	1.04–1.54
Malta ^c	27,161	67	66	55.9	1.18	0.91–1.50
South America ECLAMC	508,889	1,474	1,440	1,296.5	1.11	1.05–1.17
Czech Republic	357,203	748	612	574.8	1.06	0.98–1.15
Sweden	412,552	1,175	1,014	972.8	1.04	0.98–1.11
Western Australia	97,751	303 ⁽¹⁾	238	234.2	1.01	0.89–1.15
Finland	227,918	680	563	569.7	0.99	0.91–1.07
Australia Victoria	271,829	869 ⁽²⁾	680	689.6	0.99	0.91–1.06
Wales	107,598	296	250	253.6	0.98	0.87–1.11
Hungary	346,544	720	615	624.4	0.98	0.91–1.07
Canada Alberta	147,942	381	317	326.3	0.97	0.87–1.08
USA Utah ^c	189,151	348	320	354.1	0.90	0.81–1.01
Russia Moscow ^d	142,511	249	246	272.7	0.90	0.79–1.02
France REMERA ^e	226,741	587 ⁽³⁾	475	544.1	0.87	0.80–0.95
Ukraine	62,017	106	102	117.9	0.87	0.71–1.05
Ireland Dublin	91,644	221	204	246.7	0.83	0.72–0.95
USA Atlanta ^c	176,598	396 ⁽⁴⁾	355	430.5	0.83	0.74–0.91
Norway	239,123	473	426	516.8	0.82	0.75–0.91
Slovak Republic	165,472	243	235	286.0	0.82	0.72–0.93
Germany Saxony Anhalt	59,001	112 ⁽⁵⁾	95	116.6	0.82	0.66–1.01
USA Texas	1,088,970	1,970	1,864	2,354.2	0.79	0.76–0.83
USA California	176,427	324 ⁽⁶⁾	304	392.5	0.77	0.69–0.87
Northern Netherlands	86,898	157 ⁽⁷⁾	139	185.2	0.75	0.63–0.89
Israel IBDSR	87,340	149	134	197.3	0.68	0.57–0.80
Mexico RYVEMCE ^d	58,961	84	81	121.9	0.66	0.53–0.83
Italy Emilia Romagna	141,842	314 ⁽⁸⁾	252	398.3	0.63	0.56–0.71
Italy Lombardia	39,994	64	57	106.3	0.54	0.40–0.69
Italy Sicilia	75,600	106	92	181.5	0.51	0.41–0.62
Italy Toscana	124,169	219	169	345.6	0.49	0.42–0.57
Italy Campania	225,142	317	264	544.3	0.49	0.43–0.55
Japan JAOG	363,966	396	377	819.6	0.46	0.41–0.51
Iran TRoCA	55,260	17	17	116.1	0.15	0.09–0.23

aOE, adjusted observed–expected ratio.

ECLAMC, Latin-American Collaborative Study on Congenital Anomalies; IBDSR, Israel Birth Defects Surveillance Program; JAOG, Japan Association Obstetric and Gynecology; REMERA, Rhone-Alps Registry of Congenital Anomalies; RYVEMCE, Mexican Registry and Epidemiologica Surveillance of Congenital Malformations; TRoCA, Tabuz Registry of Congenital Anomalies.

^aObserved (Obs) total cases include livebirths (LB), stillbirths (SB) and elective terminations of pregnancy.

^bObserved livebirths cases adjusted (adj) include livebirths and elective terminations of pregnancy “adjusted” for spontaneous fetal losses for those surveillance programs where elective terminations of pregnancy are permitted.

^cAvailable years: Chile Maule, 2002–2005; Malta, 1999–2007; USA Utah, 2001–2006; USA Atlanta, 2000–2004.

^dP-value for heterogeneity among the four 5-year maternal age groups.

^eFifty-two elective terminations of pregnancy >24 week not computed in the adjustment for fetal losses.^(1–8) Calculated by assuming that livebirths, stillbirths or elective terminations of pregnancy of unknown maternal age had the same age distribution as those of known maternal age: (1) 2 cases of unknown maternal age, (2) 75 cases, (3) 66 cases, (4) 1 case, (5) 4 cases, (6) 34 cases, (7) 2 cases, (8) 4 cases.

as livebirths if allowed to continue. Note that this adjustment is not needed for programs where ETOP are illegal.

From these figures one can compute the *adjusted* observed versus expected (aOE) ratio by maternal age. In this report we focused on the maternal age range from 25 to 44 years because the published data on SFL rates are available only for this age range. Also, this age range includes most reported cases of DS, and the sample size in many surveillance programs for ages outside of this range are too small for precise estimations. The steps in computation, with examples, are detailed in Appendix 1.

Statistical Methods

Adjusted observed versus expected ratios of livebirths with DS were computed for each program for the age range 25–44 years maternal age. We used the 95% confidence interval (CI) to identify programs with potential under-registration (upper confidence limit <1.0) or over-registration (lower confidence limit >1.0). Statistical analyses were done with Stata software, version 10.0 [StataCorp, 2007]. Heterogeneity of the aOE ratios by 5-year maternal age strata was evaluated using the Breslow–Day test

[Breslow and Day, 1987], with a threshold for heterogeneity set at $P < 0.10$.

RESULTS

For each surveillance program in the study, Table II shows the number of births monitored by the program, the crude number of observed DS cases (livebirths, stillbirths, ETOP), and the adjusted number of DS livebirths taking into account the expected SFL (for programs who report ETOP). The table also shows the expected number of DS livebirths based on the published reference rates by Hook et al. and the aOE ratios with the 95% CI. As noted in the Methods Section, these data relate to the population of women between 25 and 44 years of age. Figure 1 illustrates the range of aOE and confidence intervals, sorted by descending aOE ratios.

Of the 32 programs, 13 had an aOE ratio consistent with 1 (i.e., 1 was included in the 95% CI of the aOE) and ranged from 1.18 to 0.82 (Malta, Czech Republic, Sweden, Western Australia, Australia Victoria, Hungary, Wales, Canada Alberta, Finland, USA Utah, Russia Moscow Region, Ukraine, and Germany Saxony Anhalt). Two programs, both from Latin America (Chile Maule and ECLAMC) had a statistically elevated aOE (1.27 and 1.11, respectively) and 17 had a statistically decreased aOE (from 0.87 to 0.15). Statistical evidence of heterogeneity by maternal age strata was noted in Mexico Mexican Registry and Epidemiological Surveillance of Congenital Malformations (RYVEMCE) ($P = 0.04$) and Russia Moscow ($P = 0.03$). In Mexico RYVEMCE, the aOE ratio was close to 1 for maternal ages below 35 years, but low at higher ages (0.57 in the 35- to 39-year group, and 0.32 in the 40- to 44-year groups). In Russia Moscow, the aOE was consistent at 0.75 in the age groups 25–29, 30–34, and 40–44 years, but increased (1.33) in the 35- to 39-year maternal age group. All the other 30 registries did not show evidence of heterogeneity ($P > 0.25$).

DISCUSSION

In the present article we have described a novel, simple, and inexpensive method to evaluate the validity of DS rates in birth defects surveillance program. The method is based on the fairly well-accepted assumption that maternal age-specific rates of DS are unaffected by temporal, ethnic, geographical, or environmental factors [Carothers et al., 1999]. Such stability of rates provide a common, robust basis for estimating the expected theoretical occurrence of DS in a surveillance program, once maternal age is taken into account appropriately. Potential exceptions to the stability of maternal age specific rates have been proposed, but not conclusively demonstrated, for Israeli Jews of non-European origin [Hook and Harlap, 1979], US-Hispanics [Hook et al., 1999], and African Americans [Carothers et al., 1999]. Because of the similarity of maternal age-specific rates across high-quality surveys in western countries, these estimates are currently being used in many parts of the world when calculating risks in prenatal screening programs for DS [Hecht and Hook, 1996; Bray et al., 1998; Morris et al., 2003]. These rates, which have been estimated by single year of maternal age, can be used to generate a “reference standard” for the expected number of cases of DS within a surveillance program, once the distribution of maternal age in the underlying population is

adequately known. The rate of SFL is also well known and can be incorporated in the estimates of the expected rate. Differences between the observed rate and the expected rate of DS may be due one of two factors: (a) a methodological problem of the registry (ascertainment, reporting, or registration); or (b) a real, biologically meaningful difference in DS risk. Obviously the first possibility must be strongly excluded before considering the second one.

Alternative methods can be used to evaluate the validity of DS rates. Many are based on an active search of cases in the same population, parallel or after reporting to the surveillance program, [Métneki and Czeizel, 2005; Melve et al., 2008; Savva and Morris, 2009]. However, these methods can be expensive and time-intensive, the data sources may not be available, and could themselves have methodological problems (e.g., under-ascertainment, under-registration, over-registration). The stability of rates of DS (by single year of maternal age) is a special situation in which expected rates can be computed with an unusually high degree of confidence. When resources are lacking, the method we proposed may represent the only practical possibility to evaluate validity. Even when resources are available for an additional active search of cases, the proposed method is still recommended because it provides a benchmark to measure the improvement due to the additional search and can signal a potentially real increase of DS in that population.

Using recent data from a large, international sample of surveillance programs from the International Clearinghouse, we have tested the method and shown the feasibility of a simple, novel method to evaluate the validity of reporting of DS that takes into account reported rates of ETOP and SFL, and that can be done effectively at minimal cost.

We also report findings that highlight certain patterns of ascertainment that can be valuable to know when using these data on DS for public health research and policy. For example, in several programs (13 in this study), the reported registration of DS among livebirths appears to be valid, based on the adjusted OE ratio. This was true even in the presence of marked variation in acceptance of clinical diagnosis for registration (Table I), screening policies for DS, and frequency of ETOP (data not shown, available on request). For example, the frequency of reported ETOP ranged from none in Malta (where ETOP are illegal), to fairly low in USA Utah (9%), to very high in Western Australia (61%) and Czech Republic (68%), suggesting that the methodology we used to adjust for the SFL is reliable.

Possible Explanations for High and Low aOE Ratios

There are several possible explanations for why some programs appear to over-register or under-register DS cases among livebirths. Over-registration (suggested by statistically elevated aOE ratios) is difficult to explain. It could be due to errors in coding or to random variation. For example, the highest aOE in the study was found in Chile-Maule (aOE 1.27; 95% CI 1.04–1.54), but it appears that DS rates are lower when considering a longer period of observation [Canessa, unpublished work, May 2009]. Selection bias is another possibility. For example, the other statistically significant increased aOE ratio was observed in South America ECLAMC (aOE 1.11, 95% CI 1.05–1.17). A similar finding was

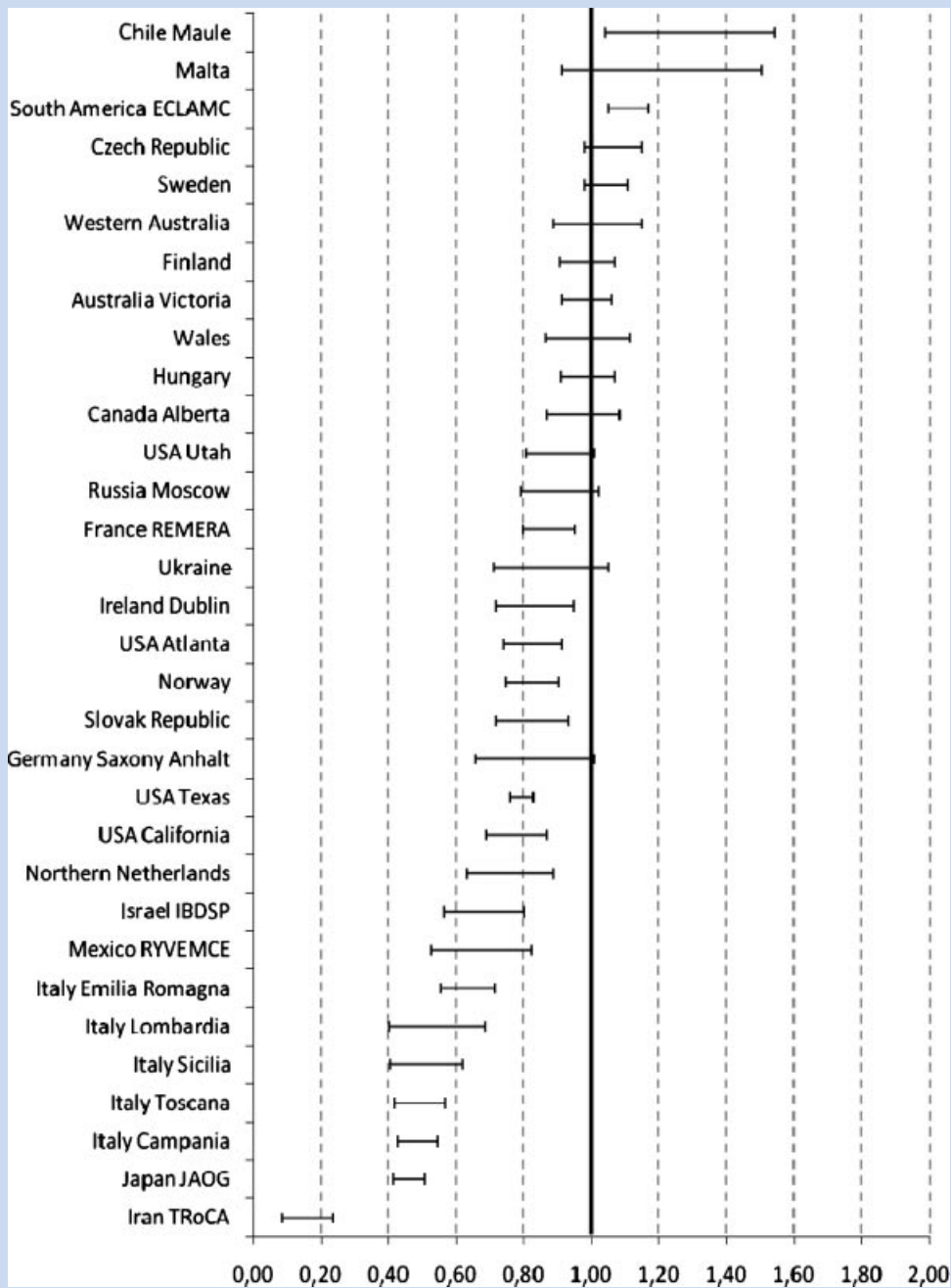


FIG. 1. Down syndrome adjusted observed–expected (aOE) ratio for the maternal age 25–44 years among 32 surveillance program members of the International Clearinghouse for Birth Defects Surveillance and Research—ICBDSR (2001–2005). Note to the figure: ECLAMC, Latin-American Collaborative Study on Congenital Anomalies; IBDSP, Israel Birth Defects Surveillance Program; JAOG, Japan Association Obstetric and Gynecology; REMERA, Rhone-Alps Registry of Congenital Anomalies; RYVEMCE, Mexican Registry and Epidemiologic Surveillance of Congenital Malformations; TRoCA, Tabriz Registry of Congenital Anomalies.

reported previously in this program [Carothers et al., 2001] in that reported rates (actually, observed vs. expected index values, similar to aOE ratios) were found to increase over time, from 1967 to 1997. A selection bias could occur in principle if fetuses identified prenatally with a condition associated with DS (e.g., nuchal translucency, heart defect, duodenal atresia) were then referred to the

select group of hospitals included in the hospital-based surveillance program. This hypothesis was also suggested by ECLAMC staff when interpreting the finding of an apparent cluster of oral clefts in the program [Poletta et al., 2007]. Alternatively, the increase may be real, if in fact women of Hispanic ethnicity have higher rates of DS-affected pregnancies [Carothers et al., 1999; Canfield et al., 2006].

Low aOE ratios, observed in the other 17 surveillance programs, suggest the possibility of under-registration. Of these programs, one (Norway) has published a validation study for DS of cases registered in the year 2001–2005 using the alternative method of active search of cases in external sources [Melve et al., 2008]. In this program, the method estimates a sensitivity of 81% (95 CI 78.3–84.6%), which is very close to the 0.82 aOE ratio in the current report (95% CI 0.75–0.91). This unique comparison between methods is very helpful, and the concordance between the findings is encouraging. Another surveillance program (USA Atlanta) published their evaluation of the program's ascertainment sensitivity for birth defects as a group for the year 1995 [Honein and Paulozzi, 1999] and their finding (sensitivity of 86.9%; 95% CI 80.6–91.9%) agrees well with the aOE ratio for DS in this report (aOE, 0.83; 95 CI, 0.74–0.91). This finding suggests that the validity of DS prevalence may be a useful indicator of the validity of ascertainment for at least some other birth defects in the same program.

Under-registration may be an issue in programs, such as in the Netherlands, in which written informed consent is required for inclusion in the surveillance programs. A recent study from the Netherlands [Weijerman et al., 2008] reported a prevalence of liveborn children with DS of 16 per 10,000 for 2003. By comparison, the reported rate in the present study from the Northern Netherlands was 11.5 per 10,000 (113/98,579). This rate is 29% lower than in the other Dutch study and, again, is consistent with the 25% estimate of under-registration based on the aOE ratio (aOE = 0.75, 95% CI 0.63–0.89) computed with the method here described.

In countries where ETOP are illegal, as in Ireland, but likely still occur (there is anecdotal evidence of women traveling abroad for ETOP), one would expect some degree of under-ascertainment, reflected in a low aOE ratio (in Ireland, aOE = 0.83). Perhaps related to this issue is the finding from Mexico RYVEMCE that the aOE ratios were low only in women above 35 years of age. This could occur if prenatal diagnosis was done more intensively in this age group, followed by illegal or unrecorded ETOP. In fact, the number of illegal and unreported ETOP in Mexico is estimated to be very high [Juarez et al., 2008]. In Japan, the very low aOE (0.46, 95% CI 0.41–0.51) is likely due to the hospital-based structure of the program, which does not capture ETOP.

Of note is also the finding of consistently low aOE ratios in all five surveillance programs from Italy (range, 0.49–0.63). There could be two possible explanations: (a) ETOP with DS could be under-reported, particularly for diagnosis occurring early in pregnancy or done outside the program's catchment area; (b) livebirths with DS could be under-reported, as suggested by a recent analysis in Italy Campania in 2006 where comparing registry and hospital discharge data indicated a 67% under-notification of livebirths with DS to the registry [Scarano, unpublished data, May 2009].

Some US programs (Atlanta, California, Texas), although not all (Utah), have low aOE ratios, and the reason for this finding is unclear. It could be due in part to missed ETOP, either because they occurred outside of the program's catchment areas or in clinics not part of the ascertainment system. Utah may have better ascertainment because of its intensive program, lower rate of ETOP, and the statewide structure of the program. Whether or not ethnic background influences the lower reported rates from the three programs is unclear. Some reports suggest that persons of African American

background have lower rates of DS [Carothers et al., 1999], and that persons of Hispanic ethnicity have higher rates [Hook et al., 1999], but this would only amplify the extent of under-reporting at least in California and Texas, where the proportion of Hispanic women is high.

Strengths and Limitations

Strengths of this analysis include the large and varied sample of surveillance programs, the use of careful adjustment by maternal age (single year), the incorporation of estimates of SFL, and the focus on the age range where most cases occur (25–44 years) and therefore less influenced by random variations due to small sample size. Evaluating DS rates by single year of maternal age is crucial to minimize confounding by maternal age, which can be a major factor when comparing populations with different maternal age distributions [Hecht and Hook, 1994]. Adjustment for SFL is also important, since in some areas a large proportion of DS pregnancies is diagnosed prenatally and many pregnancies are terminated. Focusing on the maternal age range from 25 to 44 years provides a well-characterized, large sample of pregnancies for which reference standards for maternal age and SFL are available and robust.

Limitations include the use of 5-year (instead of single year) maternal age intervals in six registries. We were able to obtain finer estimates in three Italian surveillance programs using regional data from official statistics. To evaluate this process, in some programs (Italy Tuscany, Italy Emilia Romagna, Norway, and Finland), we were able to use both methods and observed very similar results. Another limitation was the use of week ranges, rather than the exact week, of the time of prenatal diagnosis. For the timing of ETOP we had available only two categories (<16 weeks; 16 weeks or more). For programs in which there typically may be a long gap between diagnosis and ETOP (particularly for late ETOP, between 20 and 24 weeks), our method would have over-adjusted for SFL. If so, the effect is likely quite small. In the France Rhone-Alps Registry of Congenital Anomalies (REMERA), we did not adjust for the 52 TOP cases terminated after 24 weeks of gestation. Finally, another potential limitation is that published reference data for single-year maternal age DS rates and for SFL rates are available only for Western white women. When specific data become available for other racial-ethnic groups, these can easily be incorporated in the analysis.

Conclusions and Implications

Evaluating the validity of birth defects data is crucial for the appropriate use of these data in clinical and public health research and policy. As birth defects as a group become an increasingly important driver of pediatric morbidity and mortality, the need for accurate, valid data also increases. Birth defects surveillance programs are a key and sometimes only source for these data, but typically operate with limited resources. Validity studies as those presented in this report help focus on areas of improvement, where additional resources and support are needed to improve data collection and data quality.

One benefit of the approach proposed here is that it requires only limited additional effort and can be used in any surveillance

program where the distribution of cases and total births by single maternal age is available. Adjusting for SFL is essential in those surveillance programs where ETOP are allowed and common. This approach provides a single, simple parameter (adjusted OE ratio) that can help to better interpret rates, estimate the degree of under- and over-registration of cases, and compare programs nationally and internationally. In turn, this information can be a starting point to help to improve surveillance programs and ultimately promote the appropriate use of data for public health. To the extent that DS registration reflects the more general operation of a surveillance program, the validity of DS registration may be also a good initial indicator of the accuracy of data on other birth defects in surveillance programs.

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APPENDIX A. Worksheet to compute aOE ratio

Down syndrome cases

Maternal age	Total births	Down syndrome cases					Ref: derived rates of livebirths with DS ^a	Ref: estimated rates (%) of fetal loss CVs ^b	Ref: estimated rates (%) of fetal loss AMNIO ^b	Estimated number of fetal losses	Total LB cases adjusted [a0]	Expected LB cases (E)	aOE Ratio
		Total cases	ToP < 16 weeks	ToP ≥ 16 weeks	Stillbirths	Livebirths				$k_i = \frac{[e_{ji}]}{100} + \frac{[d_{ji}]}{100}$	$l_i = c_i - f_i - k_i$	$n_i = b_i h_i / 1,000$	
a _i	b _i	c _i	d _i	e _i	f _i	g _i	h _i	i _i	j _i				$\alpha_i = l_i / n_i$
25	5,600	4	1	2	0	1	0.80	23	19	0.6	3.4	4.5	0.76
26	6,500	5	3	0	0	2	0.84	24	20	0.7	4.3	5.5	0.78
27	6,800	9	3	1	0	5	0.90	24	20	0.9	8.1	6.1	1.32
28	9,000	7	0	0	1	6	0.97	25	21	0.0	6.0	8.7	0.69
29	8,900	12	2	3	0	7	1.07	26	21	1.2	10.9	9.5	1.14
30	9,200	13	5	2	1	5	1.19	27	22	1.8	10.2	10.9	0.93
31	8,800	16	6	4	0	6	1.35	28	23	2.6	13.4	11.9	1.13
32	8,300	21	8	5	0	8	1.57	29	23	3.5	17.5	13.0	1.35
33	7,800	17	6	5	1	5	1.87	30	24	3.0	13.0	14.6	0.89
34	7,000	23	7	6	2	8	2.27	31	24	3.6	17.4	15.9	1.09
35	5,500	22	6	8	3	5	2.81	32	25	3.9	15.1	15.5	0.98
36	4,600	19	8	4	0	7	3.56	33	26	3.7	15.3	16.4	0.94
37	3,700	28	8	9	2	9	4.60	34	26	5.1	20.9	17.0	1.23
38	2,600	24	11	5	1	7	6.03	35	27	5.2	17.8	15.7	1.14
39	2,100	19	7	9	0	3	8.00	36	28	5.0	14.0	16.8	0.83
40	1,500	26	7	9	2	8	10.68	38	29	5.3	18.7	16.0	1.17
41	1,000	18	6	4	1	7	14.29	39	30	3.5	13.5	14.3	0.94
42	550	10	2	4	1	3	19.06	40	30	2.0	7.0	10.5	0.67
43	350	6	1	3	0	2	25.21	41	31	1.3	4.7	8.8	0.53
44	200	6	3	2	0	1	32.86	43	32	1.9	4.1	6.6	0.62
25-44	100,000	305	100	85	15	105				54.9	235.2	238.2	0.99
25-44	$\sum b_i$	$\sum c_i$	$\sum d_i$	$\sum e_i$	$\sum f_i$	$\sum g_i$			$\sum k_i$	$\sum l_i$	$\sum n_i$	$\sum \alpha_i$	

LB, livebirths.
An excel spreadsheet to be used for calculations is available at: <http://www.icbdsr.org/page.asp?p=20702&l=1>.
^aData from Hecht and Hook [1996]. Derived rates per 1,000 livebirths (LB) with Down syndrome, by single year of maternal age [Table II].
^bData from Savva and Morris [2009]. The fetal loss rate between chorionic villus sampling (CVS) and term, and amniocentesis (AMNIO) and term, estimated by following up prenatally diagnosed cases of Down syndrome [Table I].